Interaction between C-reactive protein and cognitive functions according to APOE gene polymorphism in post-menopausal women

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Abstract

Introduction: A potential factor increasing the risk of the development of cognitive impairment with age is apolipoprotein E (APOE) ε4 carrier status. A subsequent factor which may increase the risk of development of cognitive impairment at an older age is the concentration of C-reactive protein (CRP). The objective of the study was to examine the relationship between cognitive functions and the concentration of CRP in post-menopausal women who were carriers of particular apolipoprotein E gene (APOE) polymorphisms.

Material and methods: A group of 402 women was recruited to the study. The inclusion criteria were: minimum two years after the last menstruation, follicle-stimulating hormone (FSH) concentration 30 U/ml, no dementi signs on Montreal Cognitive Assessment (MoCA). The computerized battery of the Central Nervous System Vital Signs (CNS VS) test was used to diagnose cognitive functions. APOE genotyping was performed by multiplex PCR. The blood plasma CRP levels were determined. Statistical analysis was performed using Statistica software.

Results: The level of neurocognitive index (NCI) and cognitive functions in post-menopausal women depends on apolipoprotein E gene polymorphism ($p < 0.001$) and the concentration of CRP ($p < 0.05$). A negative correlation was found between CRP and NCI ($p = 0.018$), and the reaction time ($p = 0.008$) of women with APOE ε2/ε3. A positive correlation was observed between CRP and visual memory ($p = 0.025$) in women with APOE ε3/ε3, and verbal memory ($p = 0.023$) in women with APOE ε3/ε4 or ε4/ε4.

Conclusions: Apolipoprotein E gene polymorphism may modify the relationship between CRP concentration and cognitive functions in post-menopausal women.

Key words: menopause, cognition functions, apolipoprotein E gene polymorphisms, C-reactive protein.

Introduction

Reports in the area of neuropsychology have confirmed that many cognitive functions deteriorate with age. For a long time, researchers have

been interested in whether this process in women is only the result of ageing of the brain, or is associated with undergoing the period of menopause. It has been suggested that the decrease in cognitive functions after menopause may be connected with the lack of sex hormones, or other reproduction-related factors which play a protective role. In some post-menopausal women, a considerable deterioration in functioning was observed with respect to such tests as reaction time, psychomotor speed or visual-spatial tests [1, 2]. This inspires the search for factors which may be responsible, because prophylaxis and early diagnosis of cognitive impairment are of primary importance in ageing societies.

A potential factor increasing the risk of the development of cognitive impairment with age is apolipoprotein E (APOE) ε4 carrier status [3, 4]. The human APOE gene is a polymorphic protein, consisting of three alleles (ε2, ε3 and ε4) that code for three protein isoforms, known as APOE2, APOE3, and APOE4. In the human population, the APOE ε3 allele is the most frequent (50–90%), followed by APOE ε4 (5–15%), and APOE ε2 (1–15%). Mixed forms are also observed [5, 6]. The isoform APOE4 less actively protects the neurons against the effect of oxidative stress, less actively reduces the activation of microglia and astrocytes, and is associated with intensification of the inflammatory reaction. This isoform is more susceptible to proteolytic digestion than ApoE3, which leads to the accumulation of reactive ApoE4 fragments in the cytosol, damage to the cytoskeleton and degeneration of the nerve tissue [7]. The role of ApoE in the pathomechanism of cognitive impairment also consists in its participation in the metabolism and distribution of Aβ. Researchers found that the ApoE ε4 carrier status is related to increased deposition of β-amyloid in peripherally located cerebral lobar vessels [8].

The next factor which may increase the risk of development of cognitive impairment at an older age is the concentration of C-reactive protein (CRP). Some studies indicate that there is a relationship between high concentration of CRP and cognitive function impairment [9, 10], while other studies do not confirm such a relationship [11, 12]. There are also a number of hypotheses explaining the way in which the concentration of CRP has an effect on the decline of cognitive functions. Some researchers consider that it may be a direct cause-effect relationship, because the inflammatory status is engaged in the pathophysiology of cognitive impairment. This was confirmed in studies on animals, where high levels of pro-inflammatory cytokines in the brain were related to neurodegeneration. Also, an increase in the amount of proinflammatory cytokines in tissue cultures leads to activation of the microglia and damage to the neurons [13]. In addition, inflammation markers are located around amyloid-beta deposits in the brain. An alternative hypothesis concerns an indirect effect of CRP on the state of cognitive functions. It is considered that a high concentration of CRP may lead to the development of cardiovascular and cerebrovascular diseases and, in consequence, to cognitive impairment [14, 15].

Another hypothesis concerning the indirect effect assumes that a high concentration of CRP is the result of concomitant diseases caused by improper life style (e.g. obesity, cigarette smoking, inadequate diet, lack of activity, etc.). Such diseases as metabolic syndrome, type 2 diabetes, abnormal blood pressure, and abnormal lipid profile are related to a high level of inflammatory protein, which increases the risk of cognitive disorders [16–22].

The role of concentration of CRP in the development of cognitive impairment is unequivocal and may depend on the population; however, according to the researchers, further studies are necessary in order to draw final conclusions [23].

A few studies have also attempted to determine the simultaneous effect of the apolipoprotein E gene ε4 allele and the concentration of CRP on the status of cognitive functions [24, 25]. Thus, the question arises whether the apoE4 isoform, together with the specified concentration of CRP, will, through inflammatory mechanisms, increase the influence of the combined effect of inflammatory markers on cognitive disorders.

None of the studies to date have concerned the investigation of the relationships in post-menopausal women.

The objective of this study was to examine the relationship between cognitive functions and the concentration of CRP in post-menopausal women who were carriers of particular apolipoprotein E gene polymorphisms.

The following research questions were posed:
1) Do cognitive functions in post-menopausal women depend on the concentration of CRP?
2) Do the correlations between cognitive functions and the concentration of CRP in post-menopausal women depend on ApoE gene polymorphism?

Material and methods

The study was conducted in 2013–2014, at the Institute of Rural Health in Lublin, Poland. The study group comprised 402 women from the south-eastern region of the country. The criteria of enrolment in the study were: age 50–65, good general state of health, and at least complete elementary education level. Women were qualified for the study group according to clinical symptoms (minimum 2 years from the last menstrual peri-

od), and based on the criterion of the level of follicle-stimulating hormone (FSH > 30 mlU/ml). The criteria of exclusion from the study were as follows: an active cancerous disease within the period of 5 years prior to recruitment, medical history of mental diseases, including depression during the period before menopause, addiction to medicines and alcohol, and a diagnosis of a nosologic unit with the symptoms of dementia. At the stage of qualification for the study, a brief MoCA test was performed in order to include in the study patients who did not show any traits of dementia [26]. A total of 402 post-menopausal women were examined.

Diagnostic functions were evaluated using the diagnostic equipment CNS – Vital Signs (Polish version) with software by CNS Vital Signs (1829 East Franklin Street, Bldg 500, Chapel Hill, NC 27514, 919-933-0932). CNS-VS performs the following tests: Verbal Memory Test (VBM), assessment of motor speed – Finger Tapping Test (FTT), Symbol Digit Modalities Test (SDMT), Stroop Test (ST), Shifting Attention Test (SAT), and the Continuous Performance Test. CNS-VS assesses nine cognitive functions: composite memory, verbal memory, visual memory, processing speed, executive functions, psychomotor speed, reaction time, complex attention and cognitive flexibility. Based on five of these functions – composite memory, psychomotor speed, reaction time, complex attention and cognitive flexibility – the Neurocognition Index (NCI) is calculated. The computer report from the CNS-VS test provides standard scores and evaluations of each of the five cognitive functions examined according to a 5-degree scale, as well as the Neurocognition Index. These evaluations are as follows: above average (standard score greater than 109), average (90–109), low average (80–89), low (70–79), and very low (less than 70).

The respondents had blood collected for the determination of CRP three times at weekly intervals. The blood samples were immediately transported to the laboratory. The determinations were performed in a laboratory possessing accreditation. The mean value was calculated from three determinations of CRP, and this value was considered in further analyses. The normal CRP value is less than 0.5 mg/dl.

Genomic DNA was isolated from the whole blood of patients, using commercial kits for the isolation of DNA from blood (Qiagen), and the amount and purity of the genetic material isolated were measured by means of the NanoDrop spectrophotometer. In the study, the methods of genotyping were used based on the detection of differences in the nucleotide sequences of nucleotides of alleles of the APOE gene (single nucleotide polymorphism, SNP rs429358 and rs7412) accord-

ing to Yang *et al.* [27]. To investigate polymerase chain reaction (PCR) (T-ARMS PCR) and multiplex PCR (T-ARMS PCR) reactions, appropriate primers for allele-specific binding sites were used. Amplification products were detected in agarose gels after carrying out electrophoresis. In order to confirm the results, the PCR-restriction fragments length polymorphism (RFLP) reaction was performed, where the amplification product was subjected to the effect of *Hha*I restriction enzyme, and the products of digestion were visualized on polyacrylamide after performing electrophoresis, which allowed the identification of a restriction pattern typical of each genotype. In addition, the ASPC reaction (allele-specific PCR) was performed, using specific primers, where the amplification products were subjected to electrophoresis and the results of genotyping compared to the results obtained using all the methods applied. The products of amplification were sequenced, and the sequences obtained compared with the data from GenBank.

Statistical analysis

Statistical analysis was performed by means of Statistica software. Mean values (*M*) and standard deviations (SD) were calculated for continuous variables, or absolute numbers (*n*) and relative numbers (%) of occurrence of items of categorical variables. The following tests were applied: stochastic independence χ^2 or *F* analysis of variance to discover independence of the analyzed variables from the APOE gene polymorphism. Pearson's *r* correlation coefficient was calculated between the concentrations of CRP and NCI, and cognitive functions (in scores) in the total group in the study, and in three groups distinguished according to APOE gene polymorphism. In all statistical tests the level of significance was set at 0.05.

Results

The mean age of the women examined was 56.5 ±3.5. In the study group, 63 (15.67%) women were carriers of APOE ε2/ε3, 253 (62.94%) were carriers of APOE ε3/ε3, and 86 (21.39%) were carriers of APOE ε3/ε4 or ε4/ε4. The majority of the women in the study had secondary school education (181) and university education [17]. Significant differences were observed between education level and APOE polymorphism possessed. The respondents possessing APOE ε2/ε3 and ε3/ε3 polymorphism significantly more frequently had a secondary and university education, while those with APOE ε3/ε4 or ε4/ε4 more rarely had university education (Table I).

The mean CPR concentration in the group examined was 0.30 ±0.33 mg/ml. The great majority of the women examined (82.59%) had a normal CRP

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Table I. Characteristics of the study group in total and according to polymorphism of apolipoprotein E gene

| Characteristics	Categories	Total (N = 402)	ε2/ε3 (N = 63)	ε3/ε3 (N = 253)	ε3/ε4 or ε4/ε4 (N = 86)	Significance of differences	
						Test	P-value
Age [years]	Mean ± SD	56.5 ±3.5	56.4 ±33	56.6 ±3.6	56.1 ±3.6	F = 0.712	0.491
Level of education	Elementary, n (%)	13 (3.23)	1 (7.69)	4 (30.77)	8 (38.46)	χ² = 26.731	< 0.001
	Elementary vocational, n (%)	37 (9.20)	3 (8.11)	23 (62.16)	11 (21.62)		
	Secondary school, n (%)	181 (45.02)	32 (17.68)	103 (56.91)	46 (18.78)		
	University, n (%)	171 (42.54)	27 (15.79)	123 (71.93)	21 (9.94)		
CRP [mg/dl]	Mean ± SD	0.30 ±0.33	0.17 ±0.15	0.22 ±0.26	0.62 ±037	F = 74.563	< 0.001
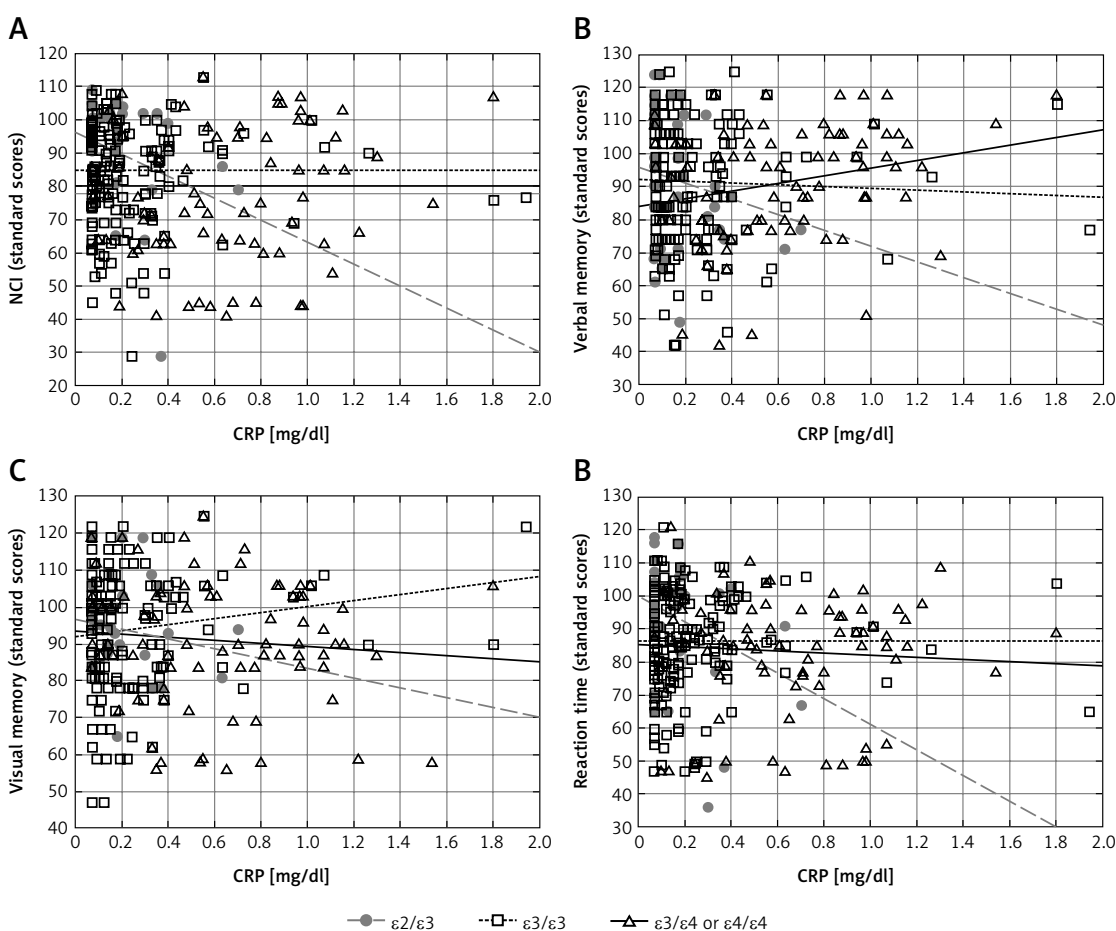
Figure 1. C-reactive protein and cognitive functions according to APOE gene polymorphism

value. The concentration of CRP significantly depended on the APOE polymorphism possessed by post-menopausal women in the study. The women possessing APOE gene ε3/ε4 or ε4/ε4 alleles had the highest level of CRP (mean value: 0.62 mg/dl), followed by those with ε3/ε3 (mean 0.22: mg/dl), while in those with ε2/ε3 this level was the lowest (mean: 0.17 mg/dl) (Table I, Figure 1).

While analyzing the numerical data concerning NCI and 9 cognitive functions (standard scores)

it was found that the poorest results were noted with respect to cognitive plasticity, processing speed, and executive functions (mean scores below 80, indicating low evaluations). The highest results were obtained by the examined women in the domains of composite memory, visual memory and verbal memory (mean scores over 90, indicating average evaluation). The women in the study obtained intermediate results with respect to complex attention, psychomotor speed and

reaction time (mean scores between 80 and 90, indicating low average evaluations) (Table II).

The occurrence of individual APOE polymorphisms was significantly associated with NCI and cognitive functions, such as executive functions, psychomotor speed, reaction time, complex attention, and cognitive plasticity. In the above-mentioned domains, women who possessed APOE ε2/ε3 alleles had the highest results, followed by those with APOE ε3/ε3 alleles, and women who were carriers of ε3/ε4 or ε4/ε4 alleles (Table II, Figure 1).

An analysis was performed to determine whether there is a correlation between NCI and cognitive functions (in scores) and concentrations of CRP (mg/dl) in blood plasma in the total number of women examined, and in groups of women distinguished according to the particular types of APOE alleles.

The concentration of CRP was negatively linearly correlated with NCI and four cognitive functions: executive functions, reaction time, complex attention and cognitive plasticity. In general, higher CPR values were accompanied by poorest results with respect to the above-mentioned functions (Table III).

In the APOE subgroups, a negative correlation was found between CRP and NCI, and the reaction time of women with APOE ε2/ε3. Generally, higher CRP values were accompanied by poorer results concerning these functions in women possessing APOE ε2/ε3 alleles. A positive correlation was observed between CRP and visual memory in women with APOE ε3/ε3, and verbal memory in women with APOE ε3/ε4 or ε4/ε4. In general, among these polymorphism subgroups, higher CRP values were accompanied by better results obtained by the women in the study with respect to the above-mentioned functions (Table III, Figure 2).

Discussion

The reason for the interest in cognitive functions in post-menopausal women is the constant increase in the average life span, which at present in Poland is 80 years. Considering the fact that the mean age at menopause is about 50 years, on average, a woman will live for 30 years during the post-menopausal period [4, 10, 28, 29]. These facts inspire the constant search for causes of the decline in cognitive functions after menopause. In order that women could obtain the highest psychophysical life comfort possible, there is a need for the development of strategies for prophylactic and therapeutic actions to prevent the occurrence of a decrease in cognitive functions or mild cognitive impairment (MCI), and consequently the development of dementia.

In our studies conducted using the battery of tests of the Central Nervous System Vital Signs (CNS VS) it was found that post-menopausal women obtained low average results with respect to cognitive plasticity, processing speed and executive functions, and with respect to NCI – complex attention, psychomotor speed and reaction time – results below average. Only in the domains of composite memory, visual memory and verbal memory were the mean values within average results. Similar data were presented by researchers from the University of California, who observed that the speed of information processing decreases during the early and late peri-menopausal period; however, according to these researchers, a decrease is also noted in verbal memory [30].

The women in the study did not show the characteristics of dementia; however, because with respect to the selected functions in the CNS VS tests the results are low and below average, probably it would

Table II. Cognitive domains (standard scores) according to polymorphism of apolipoprotein E gene

Cognitive function	Total	ε2/ε3	ε3/ε3	ε3/ε4 or ε4/ε4	Significance of differences	
	M ± 0.95 confidence interval				F	P-value
NCI	84.10 ±1.60	90.65 ±4.03	84.66 ±1.73	77.65 ±4.25	12.578	< 0.001
Composite memory	90.05 ±1.55	90.68 ±4.13	90.53 ±1.87	88.20 ±3.61	0.755	0.471
Verbal memory	91.27 ±1.75	91.32 ±4.80	91.36 ±2.18	90.97 ±3.70	0.016	0.984
Visual memory	93.12 ±1.49	94.46 ±2.93	93.60 ±1.91	90.72 ±3.54	1.432	0.240
Processing speed	79.14 ±1.40	82.51 ±3.63	78.41 ±1.77	78.81 ±2.85	2.115	0.122
Executive function	79.21 ±2.46	90.17 ±5.20	80.33 ±2.87	67.88 ±6.06	16.113	< 0.001
Psychomotor speed	83.28 ±1.79	93.46 ±3.45	82.24 ±2.02	78.86 ±4.93	13.459	< 0.001
Reaction time	86.82 ±1.61	93.05 ±4.26	86.47 ±1.87	83.30 ±3.85	6.744	0.001
Complex attention	81.58 ±2.82	92.51 ±5.70	83.79 ±3.14	67.09 ±7.63	17.404	< 0.001
Cognitive flexibility	78.07 ±2.56	89.03 ±5.74	79.27 ±2.97	66.52 ±6.28	15.153	< 0.001

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Table III. Correlation coefficients between CRP (mg/dl) and NCI, and cognitive functions (standard scores) in the total study group and according to APOE gene polymorphism

Domain	Measure	Total	ε2/ε3	ε3/ε3	ε3/ε4 or ε4/ε4
NCI	r	−0.132	−0.297	0.004	0.002
	p	0.008	0.018	0.951	0.988
Composite memory	r	0.012	−0.202	0.060	0.111
	p	0.815	0.112	0.339	0.309
Verbal memory	r	0.020	−0.178	−0.039	0.245
	p	0.687	0.162	0.533	0.023
Visual memory	r	−0.004	−0.165	0.141	−0.092
	p	0.939	0.195	0.025	0.398
Processing speed	r	−0.070	−0.219	−0.069	−0.031
	p	0.162	0.084	0.273	0.778
Executive functioning	r	−0.164	−0.205	−0.022	−0.043
	p	0.001	0.107	0.727	0.691
Psychomotor speed	r	−0.044	−0.205	0.039	0.081
	p	0.376	0.108	0.534	0.461
Reaction time	r	−0.108	−0.330	0.000	−0.067
	p	0.031	0.008	0.996	0.539
Complex attention	r	−0.154	−0.108	−0.039	0.038
	p	0.002	0.397	0.538	0.726
Cognitive flexibility	r	−0.156	−0.225	−0.022	−0.021
	p	0.002	0.076	0.733	0.851

be possible to distinguish women showing the characteristics of mild cognitive impairment according to the criteria by Petersen. It may be assumed that the majority of the women who show deficits
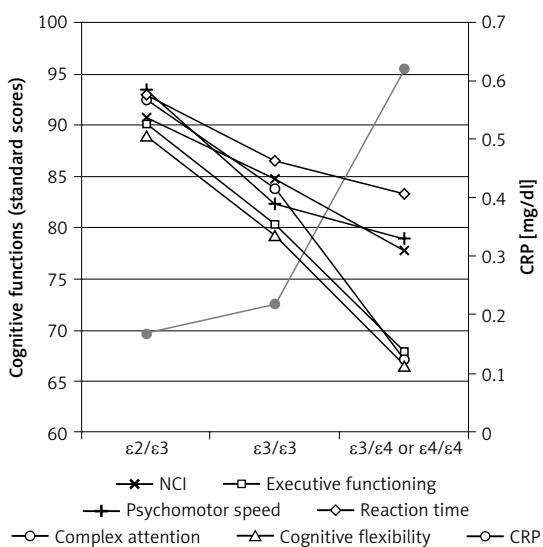

Figure 2. Scatter diagrams between CRP (mg/dl) and NCI and cognitive functions (standard scores) in the total study group and according to APOE gene polymorphism

in the CNS VS tests have only a transitory form of MCI. Nevertheless, the conversion coefficient of MCI to Alzheimer's disease is most frequently reported within the range 3–15% [31]. Mild cognitive impairment should not be ignored, because practically in all individuals with MCI, an increased risk of the development of dementia occurs [32]. This is also confirmed by the results of the WHIMS study among women aged over 65, where a cognitive deficit in at least one of the domains was present in 82.1% of respondents, and in the majority of them (74.3%) there occurred deficits in many cognitive domains [33]. The results obtained in the present study and reports from WHIMS indicate that post-menopausal women are a population exposed to a high risk of development of dementia, and indicate the need to search for additional factors which may be responsible for this situation.

The carrier state of the ε4 allele of the apolipoprotein *E* gene is a confirmed genetic risk factor of cognitive impairment at older age. Possession of the APOE gene with at least one ε4 allele increases the risk of progression of MCI to dementia [34]. Studies also show that females who are carriers of the ε4 allele of the APOE gene are at higher risk of the development of dementia, compared to males with the same forms of the APOE gene [2].

The present study confirmed that apolipoprotein E gene polymorphism was significantly related to the level of five cognitive functions (executive functions, reaction time, complex attention, psychomotor speed, cognitive plasticity) and NCI in post-menopausal women measured by the battery of computer tests CNS VS. The presence of APOE ε2/ε3 polymorphism placed the results obtained by the women in the study within the range of average or above average results. The presence of the APOE ε4 allele in a heterozygous combination (ε3/ε4) deteriorated the obtained results, and the lowest results (low or very low) were obtained by women possessing homozygous ε4/ε4 genotype. The effect of the carrier state of APOE4 on increased risk of the development of cognitive impairment in women has been confirmed by the results of other studies [35, 36]. Therefore, the investigations of APOE gene polymorphism may be a very important supplementation of the classification of patients at peri- and post-menopausal age into the groups at risk of cognitive impairment, where prophylaxis is important, and to the group where cognitive disorders are the first symptoms of the development of dementia and treatment is required [37].

Another factor analyzed in the present study which may increase the risk of the development of cognitive impairment in post-menopausal women was the concentration of CRP. This was negatively linearly correlated with NCI and four cognitive functions: executive functions, reaction time, complex attention and cognitive plasticity. This means that high CRP values were accompanied by low results with respect to the above-mentioned functions. Similar results were obtained by other researchers, where high CRP values were related to worse reaction time, complex attention, and lower psychomotor speed, but with better verbal memory [24]. Lower results concerning executive functions were also obtained in women with a higher CRP concentration [38]. A higher level of CRP was observed in the population groups with cognitive impairment [23, 39–41]. During the 4-year period of observation of the population group where the mean age was 72, the relationship between CRP concentration and decrease in cognitive functions was noted only in the first study [25]. In the group of slightly older people (over 75) a higher level of CRP was related to a decreased risk of occurrence of cognitive disorders. The researchers suggest that an elevated CRP level may have a protective effect in this age group [42]. However, other researchers indicated that sub-groups with various levels of cognitive impairment did not differ with respect to CRP concentration [43–45].

In the present study, in post-menopausal women the mean concentration of CRP was 0.31 ±0.44 pg/ml and depended on the APOE gene polymorphism ($F = 30.41$; $p < 0.01$). Women with the APOE ε3/ε3 and ε4 allele combination had a higher CRP concentration. In women with APOE ε2/ε3, higher CRP values were accompanied by lower results with respect to NCI and reaction time. In women who had APOE ε3/ε3 (with respect to visual memory), and those with APOE ε3/ε4 or ε4/ε4 (with respect to verbal memory), higher CRP values were accompanied by better results. This means that in the group of post-menopausal women in the study with APOE ε3/ε4 or ε4/ε4, and high concentration of CRP examined separately, there occurs a decrease in practically the same cognitive functions (executive functions, reaction time, complex attention, and cognitive plasticity). However, an investigation of a simultaneous effect of these two variables showed that in women with APOE ε3/ε4 or ε4/ε4 and higher CRP concentrations, statistically higher values were observed only with respect to verbal memory. These results, together with other observations, may provide evidence for the modifying role of APOE – the CRP effect on the state of cognitive functions [25]. Some researchers even suggest that individuals who have low CRP with APOE4, and high CRP but gene polymorphism other than APOE4, are more exposed to the risk of cognitive functions impairment [46].

The effect of modification of APOE ε4 in relation to CRP and the effect on cognitive functions were not observed in other studies [47]. Opposite relationships were also found. APOE ε4/ε4 was associated with a higher concentration of CRP, but worse cognitive efficacy. However, it should be emphasized that their results are doubtful and further studies are necessary [24].

In conclusion, the level of cognitive functions in post-menopausal women depends on apolipoprotein E gene polymorphism and the concentration of CRP. The lowest results were obtained by women possessing a homozygous APOE ε4/ε4 combination and higher CRP values. Apolipoprotein E gene polymorphism may modify the relationship between CRP concentration and cognitive functions in post-menopausal women.

Acknowledgments

Conflict of interest

The authors declare no conflict of interest.

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